Lightweight Noninvasive Trauma Monitor for Early Indication of Central Hypovolemia and Tissue Acidosis

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ABSTRACT

Hemorrhage is a major cause of soldier death, particularly in the first hour of injury. Seriously injured soldiers must be quickly identified and appropriate resuscitation techniques applied. Currently available vital sign measurements are inadequate for this task. In previous swine and human studies we have demonstrated that muscle oxygen measurements respond rapidly to internal bleeding and that muscle pH can be used to assess severity of injury and adequacy of resuscitation. We have developed a prototype patient monitor which noninvasively and continuously determines muscle oxygen and pH. We sought to determine whether the application of this noninvasive trauma monitor in a human model of progressive, central hypovolemia by lower body negative pressure (LBNP) would provide an early indication of impending hemodynamic instability. ***Methods****: Healthy human volunteers (30) underwent LBNP in 5 min intervals of -15, -30, -45, and -60 mm Hg, then increasing by -10 mm Hg to presyncope. Mean arterial pressure (MAP), heart rate (HR), arterial oxygen saturation via pulse oximetry (SpO_2), stroke volume (SV) and total peripheral resistance (TPR) were measured continuously and noninvasively throughout the study. Muscle oxygen saturation (SmO_2) and muscle pH (pHm) were determined noninvasively from near infrared spectra which were corrected for interference from skin pigment and fat. For each LBNP level the last 3 minutes of data were averaged for all variables. For each parameter, linear mixed model analysis was used to determine the first level of LBNP that could be distinguished statistically from baseline ($p < 0.05$).* ***Results & Discussion****: SmO_2 and SV significantly decreased during the first LBNP level (-15 mm Hg) whereas HR, MAP and SpO_2 were later indicators of impending cardiovascular collapse. SmO_2 declined in parallel with SV and inversely with TPR, suggesting, in this model, that SmO_2 is an early indicator of reduction in oxygen delivery through vasoconstriction. Muscle pH decreased later in the progression of central hypovolemia, suggesting an imbalance between oxygen delivery and demand.* ***Conclusions:*** *Spectroscopic determination of SmO_2 is noninvasive and continuous, and provides an early indication of impending cardiovascular collapse resulting from progressive reduction in central blood volume, demonstrating changes earlier than standard vital sign measurements (MAP, HR, SpO_2). This technology has the potential to help combat medics quickly and accurately triage casualties and monitor patients during lengthy transport from combat areas.* ***On-Going Developments:*** *The monitor has been miniaturized to a 58 g solid state sensor with the future capability of continuous, wireless transmission of SmO_2, pH and hematocrit values.*

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14. ABSTRACT

Hemorrhage is a major cause of soldier death, particularly in the first hour of injury. Seriously injured soldiers must be quickly identified and appropriate resuscitation techniques applied. Currently available vital sign measurements are inadequate for this task. In previous swine and human studies we have demonstrated that muscle oxygen measurements respond rapidly to internal bleeding and that muscle pH can be used to assess severity of injury and adequacy of resuscitation. We have developed a prototype patient monitor which noninvasively and continuously determines muscle oxygen and pH. We sought to determine whether the application of this noninvasive trauma monitor in a human model of progressive, central hypovolemia by lower body negative pressure (LBNP) would provide an early indication of impending hemodynamic instability. Methods: Healthy human volunteers (30) underwent LBNP in 5 min intervals of -15, -30, -45, and -60 mm Hg, then increasing by -10 mm Hg to presyncope. Mean arterial pressure (MAP), heart rate (HR), arterial oxygen saturation via pulse oximetry (SpO2), stroke volume (SV) and total peripheral resistance (TPR) were measured continuously and noninvasively throughout the study. Muscle oxygen saturation (SmO2) and muscle pH (pHm) were determined noninvasively from near infrared spectra which were corrected for interference from skin pigment and fat. For each LBNP level the last 3 minutes of data were averaged for all variables. For each parameter, linear mixed model analysis was used to determine the first level of LBNP that could be distinguished statistically from baseline ($p < 0.05$). Results & Discussion: SmO2 and SV significantly decreased during the first LBNP level (-15 mm Hg) whereas HR, MAP and SpO2 were later indicators of impending cardiovascular collapse. SmO2 declined in parallel with SV and inversely with TPR, suggesting, in this model, that SmO2 is an early indicator of reduction in oxygen delivery through vasoconstriction. Muscle pH decreased later in the progression of central hypovolemia, suggesting an imbalance between oxygen delivery and demand. Conclusions: Spectroscopic determination of SmO2 is noninvasive and continuous, and provides an early indication of impending cardiovascular collapse resulting from progressive reduction in central blood volume, demonstrating changes earlier than standard vital sign measurements (MAP, HR, SpO2). This technology has the potential to help combat medics quickly and accurately triage casualties and monitor patients during lengthy transport from combat areas. On-Going Developments: The monitor has been miniaturized to a 58 g solid state sensor with the future capability of continuous, wireless transmission of SmO2, pH and hematocrit values.

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1.0 INTRODUCTION

Trauma and severe hemorrhage remain the most frequent causes of death in the 1-44 year age group in both the civilian and military settings [1-3]. Early recognition of the severity of shock and prompt institution of appropriate resuscitative measures are widely believed to improve outcome and decrease the progression to multi-system organ failure by virtue of maintaining end-organ perfusion. Routine clinical parameters such as arterial blood pressure, heart rate (HR), mental status and urine output, as well as hematocrit levels, are often late indicators of the true extent of metabolic derangement during hypovolemic shock. In a study on HR variability and its association with mortality in pre-hospital trauma patients, Cooke and co-workers demonstrated that HR, arterial oxygen saturation (via pulse oximetry) and arterial blood pressure were poor predictors of outcome [4]. Hence, there exists a need for noninvasive, continuous monitoring of parameters that can provide an early indication of central hypovolemia.

The physiological response to hemorrhage includes significant vasoconstriction to help maintain adequate perfusion pressure to vital organs. In swine models of hemorrhage, this can be observed as an early, rapid and significant decrease in peripheral and splanchnic oxygenation [5,6] as blood is shunted to the heart and brain. Based on this known physiological response, noninvasive assessment of muscle oxygen can provide a significantly earlier indication of blood volume loss than the standard vital sign measurements.

Near infrared spectroscopy (NIRS) is in wide clinical use for the determination of arterial oxygen saturation or pulse oximetry (SpO_2), which provides information on pulmonary gas exchange. When blood flow to the peripheral muscles is decreased, an increase in oxygen extraction is reflected in a reduction in muscle oxygen saturation (SmO_2) [5] and muscle oxygen tension (PmO_2) [7] both of which can be determined noninvasively with NIRS. It is also possible to determine muscle pH (pHm) using NIRS [7,8]. In swine hemorrhage, tissue pH is significantly more sensitive to shock than measures of arterial and venous pH [6], and depressed tissue pH is strongly associated with negative outcomes [9]. From a practical standpoint, NIRS instruments can be made small and portable, allowing them to be used for rapid, noninvasive patient assessment both inside and outside the hospital.

In experiments conducted at the US Army Institute of Surgical Research, we used lower body negative pressure (LBNP) to create central hypovolemia as a model for pre-shock hemorrhage, and demonstrated that SmO_2 and PmO_2 were very early indicators of central hypovolemia for a small group of subjects [10]. Muscle oxygen was found to be significantly different from normal values at levels of simulated blood loss which were less than that detected by changes in standard vital sign measures such as HR, blood pressure and SpO_2. In this model we also demonstrated a significant reduction in pHm when muscle oxygen reached a critically low level. In the current paper we report the results from a larger group of subjects studied under the same protocol.

The NIRS monitor that was used in the LBNP study is too large and fragile for immediate battlefield and civilian pre-hospital applications. We have undertaken an effort to convert the fiber optic laboratory system to a totally solid state spectroscopic monitor targeted for field and pre-hospital use.

2.0 METHODS

2.1 Protocol

All procedures and risks associated with the study were explained to the research subjects and their voluntary written informed consent was obtained. With the use of a neoprene skirt designed to form an airtight seal

between the subject and the chamber, the application of negative pressure to the lower body (below the iliac crest) results in a redistribution of blood away from the upper body (head and heart) to the lower extremities and abdomen. This model provides conditions of controlled, experimentally-induced hypovolemic hypotension, offering a valuable method for investigating monitoring devices such as NIRS.

Each subject reported once to the laboratory for a progressive LBNP protocol. The subject was first instrumented with noninvasive devices to measure HR, blood pressure, SpO_2, stroke volume (SV), arterial blood pressure, SmO_2, and pHm. The LBNP protocol consisted of a 5-min baseline period followed by 5-min of chamber decompression to -15, -30, -45, and -60 mmHg, and additional increments of -10 mmHg every 5 min until either the onset of cardiovascular collapse or the completion of 5 min at -100 mmHg. Cardiovascular collapse was defined by one or a combination of the following criteria: (a) a precipitous fall in systolic blood pressure (SBP) >15 mmHg, and/or a sudden bradycardia; (b) progressive diminution of SBP <70 mmHg; or, (c) voluntary subject termination due to discomfort from pre-syncopal symptoms such as sweating, nausea, dizziness or grey-out. At the onset of cardiovascular collapse the chamber vacuum was released to ambient pressure in order to rapidly restore blood flow to the central compartment. To assure subject safety, an ACLS-certified physician was present in the laboratory building during all LBNP tests.

2.2 Hemodynamic Measurements

Continuous HR was measured from a standard electrocardiogram (ECG). Beat-by-beat SBP and diastolic blood pressure (DBP) were measured noninvasively using an infrared finger photoplethysmograph (Finometer® Blood Pressure Monitor, TNO-TPD Biomedical Instrumentation, Amsterdam, The Netherlands). The Finometer® blood pressure cuff was placed on the middle finger of the left hand which, in turn, was laid at heart level. Oxygen saturation was measured using pulse oximetry (BCI Capnocheck Plus; Smiths Medical, Waukesha, WI).

While the Finometer® is capable of determining SV and total peripheral resistance (TPR), superior accuracy in this setting has been observed with the thoracic bio-impendance technique [11]. Beat-to-beat SV was measured noninvasively using thoracic electrical bio-impedance with an HIC-2000 Bio-Electric Impedance Cardiograph (Bio-Impedance Technology, Chapel Hill, NC, USA). Cardiac output (Q) was calculated as the product of HR and SV, and TPR was estimated by dividing MAP by Q.

Hemodynamic data were sampled at 500 Hz and recorded directly to data acquisition software (WINDAQ, Dataq Instruments, Akron, OH, USA). Analysis of data was subsequently accomplished using commercially-available analysis software (WinCPRS, Absolute Aliens, Turku, Finland). Data presented for each of these parameters represent the average values taken over the last 3 min of baseline and each LBNP level.

2.3 Noninvasive Determination of SmO_2, PmO_2 and pHm

SmO_2, PmO_2 and pHm were determined noninvasively using a NIRS monitor developed jointly by personnel from the Anesthesiology Department of the University of Massachusetts Medical School (Worcester, MA, USA) and Luxtec Corporation (West Boylston, MA, USA). This spectroscopic technique was previously validated for individual heart surgery patients against invasive PO_2 and pH sensors inserted into the hypothenar muscle [7]. The pHm technique was validated across multiple subjects during handgrip exercise [12]. The NIRS system used in this study employed additional mathematical preprocessing techniques to correct spectra for variation in skin pigmentation, fat and muscle optical properties prior to the calculation of SmO_2, PmO_2 and pHm. These techniques are necessary to allow one calibration equation for each parameter to be used for all subjects. The optical sensor collected NIR reflectance spectra from deep within the forearm

muscle (flexor digitorum profundus) every ~20 sec. The spectra were then processed with calibration equations contained in a dedicated computer. SmO_2, PmO_2 and pHm were simultaneously calculated from each spectrum, displayed as a trend and stored on a hard drive contained in the system.

Light was collected with 2 sensors contained in the same housing. One sensor collected light which illuminated only the skin and fat layer. The second sensor collected light which illuminated the skin, fat and muscle layer. Mathematical processing removed the light reflected from the skin and fat, leaving only the absorption spectrum of muscle [13]. Removal of spectral interference from skin pigmentation and fat is critical to determining absolute chemical concentrations from muscle spectra. A detailed description of the SmO_2 calculation and its validation has recently been published by Yang et al [14]. PmO_2 was calculated from the SmO_2 determination. The same absorption spectra were also processed by the computer to calculate pHm. A second calibration equation is contained in the computer and used to calculate pHm from spectra which were corrected for subject-to-subject differences in muscle fiber structure [15]. The calibration equation was developed prior to this study in separate experiments where corrected spectra were statistically related to invasive measurements of interstitial fluid pH to produce the calibration equation [7,12].

The light output of the system was assessed with 3 NIST-traceable reflectance standards (Avian Technologies, LLC, Wilmington, OH, USA) with nominal values of 2%, 50% and 99%, prior to use on each subject to allow for determination of the absolute values of SmO_2, PmO_2 and pHm [16].

2.4 Statistical Analysis

Values for NIRS measurements and hemodynamic parameters are presented as the mean ± 1 standard error of the mean (SE). Data from all the noninvasive sensors were collected continuously. For each LBNP level, the last 3 min of data for each measured parameter were averaged to provide a single value for that level.

Each measured parameter was analyzed using a linear mixed model analysis of variance with a first order autoregressive covariance structure to determine if there was a significant variation during progressive LBNP. This type of analysis takes into account the repeated nature of the experimental design. If statistical differences were found, Bonferroni-corrected comparisons with baseline measurements were performed to determine the first level of LBNP that could be distinguished statistically from baseline ($p < 0.05$). Statistical analysis was performed using SPSS (Version 14.0, SPSS Inc., Chicago, IL, USA).

3.0 RESULTS

Complete datasets were obtained from twenty-seven (27) of the thirty (30) subjects who entered the study. Figure 1 shows that as LBNP increased there was a near linear decrease in stroke volume. Changes in mean arterial pressure (MAP) and HR during the progressive LBNP protocol are illustrated in Figure 2. Significant decreases in MAP were observed at a negative pressure of 60 mmHg, while HR was slightly more sensitive with a significant increase in HR observed at -45 mmHg. While the data is not shown, SpO_2 never changed significantly from baseline.

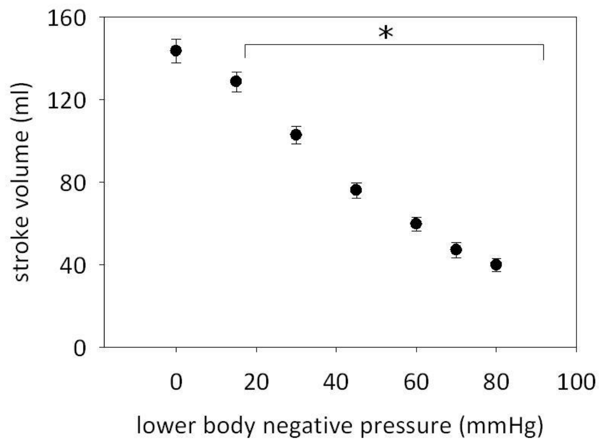

Figure 1: Stroke volume during LBNP. Mean ± SE for all subjects (N=27). Negative pressure is increased progressively from baseline (0). * levels significantly different from baseline, p <0.05.

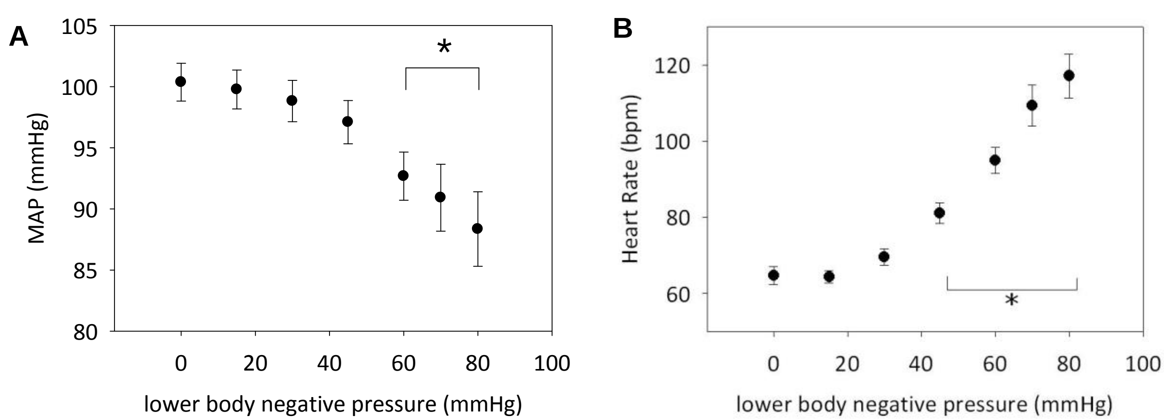

Figure 2: (A) Mean arterial pressure (MAP) and (B) Heart Rate during LBNP. Mean ± SE for all subjects (N=27). Negative pressure is increased progressively from baseline (0). * levels significantly different from baseline, p <0.05.

Figure 3 shows changes in the NIRS derived parameters during LBNP. SmO_2 decreased continually during LBNP with a significant decrease occurring at the first level of negative pressure, 15 mmHg. A significant decrease in pHm was observed at -45 mmHg.

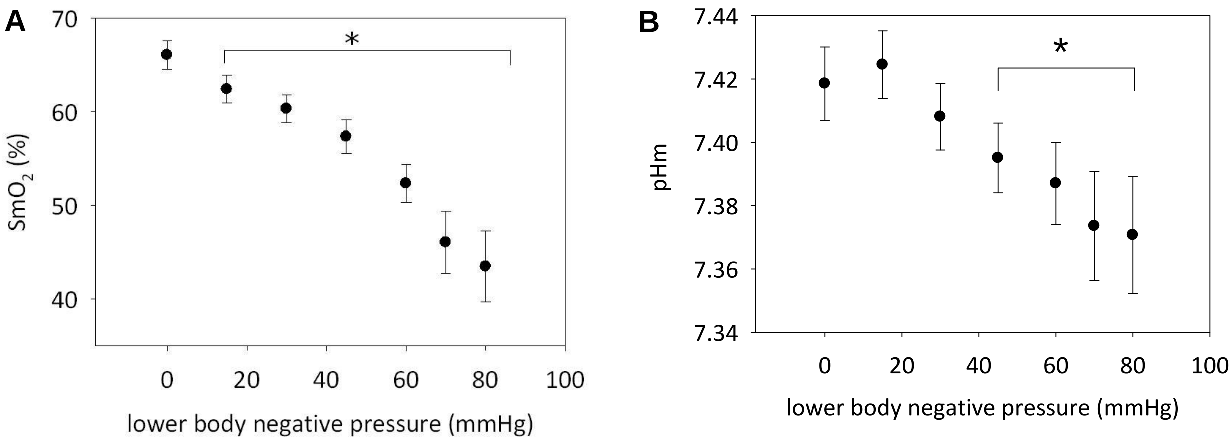

Figure 3 (A) NIRS-determined muscle oxygen saturation (SmO_2) and (B) and muscle pH (pHm) during LBNP. Mean ± SE for all subjects (N=27). Negative pressure is increased progressively from baseline (0). * levels significantly different from baseline, p <0.05.

Figure 4 illustrates the relationship of SmO_2 with stroke volume (A) and with total peripheral resistance (B). There was a strong linear relationship between SmO_2 and SV ($R^2 = 0.92$) and an equally strong inverse linear relationship between SmO_2 and TPR ($R^2 = 0.96$).

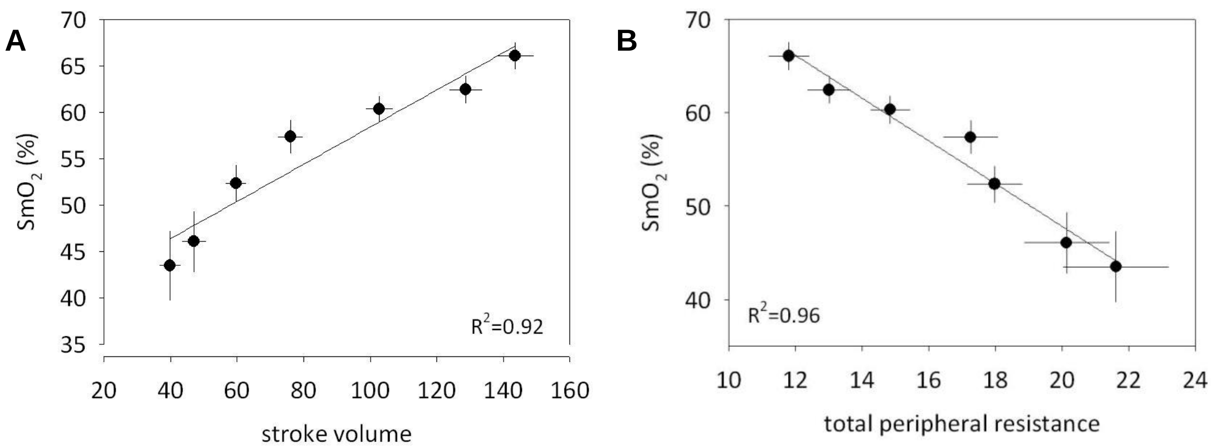

Figure 4: (A) Linear relationship between SmO_2 and stroke volume at each LBNP level. (B) Inverse linear relationship with total peripheral resistance. Mean ± SE for all parameters.

4.0 DISCUSSION

This study confirmed the findings of our initial publication which documented the results from the first ten subjects of this series [10]. Both studies demonstrated that muscle oxygen determined noninvasively with a novel NIRS methodology, was correlated with SV, and was one of the earliest indicators of progressive central hypovolemia in human volunteers. The reductions in SV, SmO_2 and PmO_2 were apparent at an LBNP level that represented an estimated blood loss of only 400-500 ml [17]. Perhaps more importantly, reductions

in muscle oxygen were detected much earlier than the standard clinical measures of HR and BP. A further finding from these studies is that a small but significant decrease in noninvasively measured pHm was observed near the same time as an increase in HR.

The observation that decreases in SmO_2 proportionately tracked the progressive fall in SV throughout the course of the LBNP protocol was observed with the first ten subjects and the correlation is equally strong with the addition of seventeen more subjects to the data set. This relationship suggests that the noninvasive SmO_2 measurement is a sensitive marker of reduced cardiac output and delivery of blood to peripheral tissues during central hypovolemia. Likewise, the inverse linear relationship between SmO_2 and TPR implies that skeletal muscle vasoconstriction and a subsequent reduction in local tissue blood flow in response to central hypovolemia is a major cause of reduced regional oxygen in this laboratory model. These observations are consistent with the work of Fadel et al who simultaneously measured relative changes in forearm oxygenated hemoglobin plus myoglobin, blood flow, and vascular conductance during LBNP between -10 and -50 mm Hg [18]. These authors showed strong correlations between NIRS changes and both blood flow and vascular conductance. Our work demonstrates that there is an inverse relationship between NIRS-determined tissue oxygenation and TPR from the earliest levels of hypovolemia to the point of presyncope.

It has been known for many years that one of the earliest compensatory mechanisms in hemorrhage is sympathetically-mediated reflex vasoconstriction [19]. During hemorrhage, vasoconstriction is heterogeneous throughout the body, predominantly affecting skeletal muscle and splanchnic circulations to redirect blood flow to the heart and brain [20-22]. Our results complement a previous suggestion that progressive LBNP simulates the acute hemodynamic responses occurring during the early stages of hemorrhagic shock [4]. One of the novel aspects of the current study is the demonstration that noninvasively determined skin and fat corrected SmO_2 can be used as an indication of this diversion of blood from the skeletal muscle [19], suggesting that it may be an early indication of hemorrhagic shock.

Figure 3B shows that pHm declined slowly until there was a large change in oxygen delivery, as evidenced by considerable reductions in SV and SmO_2. This can be seen more clearly with data from one subject, shown in Figure 5. Here pHm is plotted as a function of muscle PmO_2 for the same subject. As negative pressure increased, PmO_2 decreased, however, pHm remained stable until a critical level of PmO_2 was reached, indicating that there was insufficient oxygen available to meet the tissue's metabolic demand. We previously demonstrated a similar relationship between tissue pH and tissue PO_2 in swine liver during hemorrhagic shock [6]. In this animal study, measurements of tissue pH and PO_2 with invasive sensors demonstrated a breakpoint (PO_2crit) where pH began to decrease after tissue PO_2 had decreased to 22.3 ± 3.8 mmHg (linear model) [6], a value similar to that observed in this human study. These data provide evidence that LBNP causes a tissue metabolic disturbance (i.e., muscle dysoxia in the forearm) similar to that observed during actual bleeding.

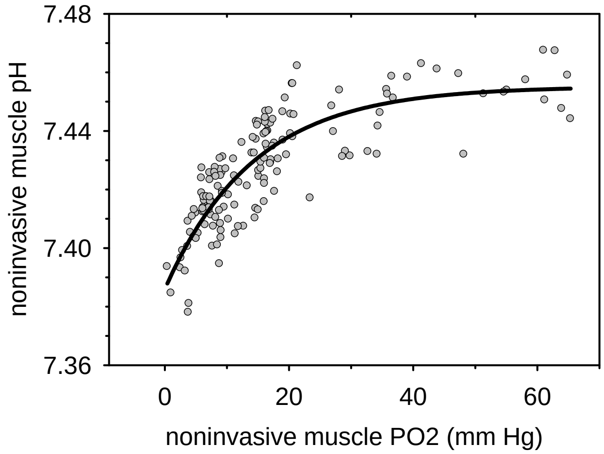

Figure 5: Relationship between muscle pH (pHm) and muscle oxygen tension (PmO_2) for one human subject undergoing LBNP protocol.

5.0 ON-GOING WORK

We have demonstrated a noninvasive technique for the determination of SmO_2, PmO_2 and pHm in a clinical laboratory model that simulates hemorrhage in humans. SmO_2 and PmO_2 were found to be early indicators of a reduction in oxygen delivery, most likely resulting from increased vasoconstriction to shunt blood from the skeletal muscle to the heart and brain. Muscle pH begins to decrease only when oxygen levels are significantly reduced, suggesting that the decrease in pHm may signal the onset of dysoxia in the muscle tissue. This noninvasive, continuous technique lends itself to monitoring critically ill patients at risk for hemodynamic instability.

While noninvasive and portable, the NIRS system used in this study employed large, cumbersome fiber optic cables. Fiber cables are fragile and the system required daily recalibration to compensate for on-going fiber breakage. Additionally, two separate cables were required, one cable for measurement of muscles with thin overlying fat layers (< 7mm) and a different cable for muscles with thicker overlying fat layers (> 7mm). This system is not suitable for operational military environments.

Reflectance Medical has recently developed a prototype for a solid state version of this NIRS sensor (Figure 6). The tungsten light source in the fiber optic system is replaced by a set of broadband light emitting diode (LED) arrays in the solid state system. The fiber system's grating spectrophotometer is replaced with a custom, fully solid state spectrophotometer with dimensions 1mm x 8mm. The fiber optic cables are completely eliminated and the sensor's optical elements are placed directly on the skin.

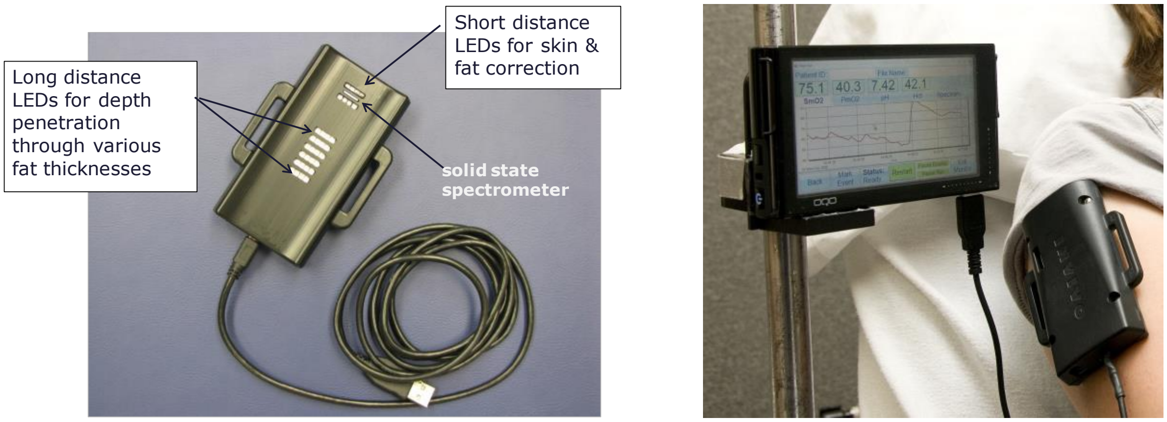

Figure 6: (A) Reflectance Medical prototype solid state NIRS sensor for simultaneous determination of SmO_2 and pHm; (B) placed on subject, running off handheld computer.

The sensor, composed of a single circuit board, weighs under 60 g and is approximately 2” x 4” when housed. The sensor contains a set of “short distance” LEDs to collect light from skin and fat layers as well as a set of “long distance” LEDs to collect light from skin, fat and muscle layers. The muscle spectrum is generated by mathematically removing the skin and fat spectral information collected with the short distance LEDs from the spectrum collected by the long distance LEDs [13]. One bank of short distance LEDs and one bank of long distance LEDs are selected automatically to accommodate a wide variety of skin pigment and fat thickness. The system is operated by a handheld, touch screen computer.

Preliminary human studies with the prototype solid state system showed equivalent performance with the fiber optic system. Evaluation of the solid state sensor in the laboratory (LBNP) and clinical setting (high blood loss orthopaedic surgery) have recently been initiated.

6.0 ACKNOWLEDGEMENTS

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